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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,562	01/26/2001	William J. Curatolo	PC9674AJTJ	8513

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/770,562	CURATOLO ET AL.	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7, 10, 11, 13, 15, 17, 22-26, 38, 39, 41-43, 45, 47 and new claims 49-52* is/are rejected.

7)☒ Claim(s) *28-37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/05/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1, 4-7, 10, 11, 13, 15, 17, 22-26, 28-39, 41-43, 45, 47 and new claims 49-52 .

DETAILED ACTION

Examiner acknowledges receipt of request for extension of time, request for continued examination under 37 CFR 1/114, request for reconsideration and remarks, all filed 3/3/06 and IDS filed 1/05/06. Claims 1, 4-7, 10, 11, 13, 15, 17, 22-26, 28-39, 41-43, 45, 47 and 49-52 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/3/06 has been entered.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 4-7, 10, 11, 13, 15, 17, 22, 39, 41-43, 45 and 47 and new claims 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (English Translation of Yakuzaigaku 53(4): 221-228, 1993).

Yamaguchi studies the solubility of solid dispersions of 4-0-(4-methoxmhenyllacetyltylosin (MAT) in carboxymethylethylcellulose (CMEC) or

hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT®) and using the solid dispersions an increase of AUC and Cmax of greater than 2.5 fold was observed achieved (abstract). Yamaguchi prepares solid dispersions of MAT in CMEC, AQOAT or EC (ethylcellulose) by spray drying (item # 2 of page 2); the solubility of crystalline MAT is determined to be 0.002 at pH 6.8 (item 1 of page 4 and Table 1). In Figure 2 and at pH 4.0, Yamaguchi shows solid dispersions of MAT and CMEC or AQOAT in a ratio of 10:1 and concentration of the MAT in a use environment from AQOAT carrier matrix is about 650 μg and the concentration of amorphous MAT without a polymer in a use environment is about 220 μg; the ratio of the MAT from the AQOAT matrix to a control, such as the one without a polymer is at least greater than 1.5 and specifically about 2.95 (see page 5 and data extrapolated from Figure 2). Although, Yamaguchi exemplifies the dissolution studies with CMEC, the Yamaguchi reference also discloses MAT with AQOAT as is seen in the abstract, pages 2 (last line) and 5, and Figure 2. MAT bulk powder is used in the study in the preparation of the solid dispersion (page 2, item #1) and powder reads on amorphous.

Yamaguchi describes oral administration, fed state (i.e. "withholding food from the beagles from the night before the study") and measuring of blood concentration (page 4, item # 7 and page 10, item # 4), which description confers the implication of gastrointestinal tract environment and thus, this aspect of the disclosure reads on gastrointestinal tract use environment. Although, item #4 of page 10, specifically directs the investigation to MAT/CMEC, this particular disclosure is an exemplification of the MAT solid dispersion, and since the abstract and last line of page 2 and then page 5 disclose MAT/AQOAT solid dispersions, page 10, item #4 would apply to the MAT/AQOAT dispersion. Specifically,

paragraph 2, page 2 of translation states " MAT (100 g) and 50 g, 20 g,10 g or 5 g of CMEC were dissolved in 300 ml, of a 1:1 solvent mixture of methylene chloride and ethanol, then spray-dried (SD-1; Tokyo Rikakikai) at an inlet temperature of 120 °C to form a powder. **Preparation was similarly carried out using AQOAT®** or EC as the carrier." Thus drug: polymer ratios of from 2:1, 5:1, 10:1 and 20:1 are disclosed.

The difference between Yamaguchi and the instant claims is that Yamaguchi is silent on the amount of residual solvent present after the spray drying process. However, it is the Examiner's position that since the prior art does not explicitly disclose that there is zero residual solvent present or greater than 10 wt% residual solvent present after spray drying, it is reasonable to expect that some amount of solvent is left after spray drying and the person of ordinary skill in the art would have the technical know how to determine residual solvent left after spray drying. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare solid amorphous dispersion by drying. In the absence of a showing, specifically indicating that the spray dried dispersion of the prior art contains no residual solvent or greater that 5% residual solvent and a showing that unexpected results is provided by the less than 5% residual solvent, a solid dispersion having less than 5% residual solvent is not patentable over the prior art dispersion that is essentially the same except for silence in residual solvent.

Response to Arguments

Applicants argue Yamaguchi teaches away from the invention because Yamaguchi does not disclose homogeneous dispersion and that Differential Scanning Calorimetry performed by applicants in the declarations demonstrates that the higher the drug load is in a dispersion, the more likely it is that the dispersion will contain distinct drug phase and that for Yamaguchi

"higher drug loading correlate with higher dissolved drug concentrations," and that for the examined application as per Friesen's declaration, concentration is enhanced by lowering the drug loading.

3. Applicant's arguments filed 3/3/06 have been fully considered but they are not persuasive.

The claim 1 is a product claim. The prior art discloses solid amorphous dispersion, Yamaguchi prepares the solid dispersion by spray drying and applicants form the molecular dispersion by spray drying. Thus the dispersion of Yamaguchi formed by spray drying is molecularly dispersed. Specifically, the only mention of "molecularly dispersed" in the examined application is in paragraph 0027 of the published application where it states, "it is generally preferred for the drug to be molecularly dispersed such that there is little or no drug present as separate amorphous domains." Yamaguchi does not state that the dispersion is heterogeneous. Yamaguchi, which forms solid amorphous dispersions of a drug by spray drying as does the instant application, does not mention that the drug is present as separate amorphous domains. It is logical to expect that if one spray dried product dries up within a certain time, them the another spray dried product would be reasonable expect to dry within the same time frame. It is further noted that both the prior art reference and the instant claims prepare the solid dispersions by spray drying. The claims are directed to compositions and the process of preparing the dispersions in both the examined claims and the prior art are the same. Applicants provided no showing indicating that the particles of Yamaguchi solidified in longer than 5 seconds and there is no unexpected results showing that the dispersion of the prior art formed by

spray drying as does the claimed invention differs in any way from the claimed solid dispersion. And the declaration has not shown that.

4. Claims 1, 7, 11, 13, 15, 23-26, 38, 39, 41-43, 45 and 47 and new claims 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyajima et al. (US 4,983,593).

Miyajima discloses a pharmaceutical composition that comprises 5-(5,5-dimethyl-1,3,2- dioxaphosphorinane-2-yl)-l,4-dihydro-zy6-dimethyl-4- (3- itrophenyl)-3-pyridine carboxylic acid 2-(phenylmethyl)amino) ethyl ester P-oxide hydrochloride-thanol (NZ-105) and hydroxypropylmethylcellulose acetate succinate (HPMCAS or AQOAT) in a 1:1 ratio (abstract) and column 4, lines 6-8 discloses NZ-105/HPMCAS composition where the amount of the HPMCAS is 1-7 parts by weight per unit of NZ-105. Miyajima's composition further comprises filers, binders, lubricants and disintegrants (column 4, lines 22-47). Miyajima's composition is formulated as powders, granules, tablets, capsules or pills (column 4, lines 16-21). Powder or particles of NZ-105 and HPMCAS are produced by vacuum drying, spray drying or freeze-drying (column 3, lines 55-6%. While nicardipine and nifedipine are disclosed by Miyajima in the background section as well known 1,4-dihydropyridine-type compounds that are poorly soluble in water and can be prepared as amorphous formulations, the nicardipine and nifedipine are different compounds from the compounds recited in instant claims 29, 30, 32, 34 and 36. Instant claim 37 recites nifedipine as a drug. Examples 1-4 of Miyajima disclose NZ-105/HPMCAS composition where the ratio of the NZ-105 to the HPMCAS is 1:3. Miyajima is silent with respect to the solubility of the drug NZ-105 in a use environment or oral administration or administration to a fasted animal. However, the solubility of the drug is an

inherent property of a drug and would appear to be an inherent property of the NZ-105/HPMCAS compositions. It is noted that no specific drug is claimed in the claims in question.

There is no demonstration in applicants' specification that the recited particle sizes provide unusual results. In the absence of a showing the particles having the recited particle sizes in claims 23-26 is not patentable over particles of the prior art. Regarding claim 38, Miyajima's disclosure of nifedipine as poorly water-soluble drug whose solubility can be improved would motivate a person of ordinary skill in the art to prepare a product containing nifedipine in order to improve the solubility

The difference between Miyajima and the instant claims is that Miyajima is silent on the amount of residual solvent present after the spray drying process. However, it is the Examiner's position that since the prior art does not explicitly disclose that there is zero residual solvent present or greater than 10 wt% residual solvent present after spray drying, it is reasonable to expect that some amount of solvent is left after spray drying and the person of ordinary skill in the art would have the technical know how to determine residual solvent left after spray drying. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare solid amorphous dispersion by drying. In the absence of a showing, specifically indicating that the spray dried dispersion of the prior art contains no residual solvent or greater that 5% residual solvent and a showing that unexpected results is provided by the less than 5% residual solvent, a solid dispersion having less than 5% residual solvent is not patentable over the prior art dispersion that is essentially the same except for silence in residual solvent.

Response to Arguments

Applicants argue that Miyajima mentions spray drying only once in the entire disclosure, that Miyajima fails to describe solidification time of less than 5 seconds, that Miyajima does not disclose residual solvent and that Miyajima fails to disclose amorphous drug. Furthermore, applicants refer to excerpt from Remington that spray drying does not necessarily produce amorphous drug.

5. Applicant's arguments filed 3/3/06 have been fully considered but they are not persuasive.

The Remington reference does state that spray drying leads to "crystals and/or amorphous solids depending on the rate and conditions of solvent removal." Thus, the Remington reference further supports the fact that spray drying leads to amorphous products. It is respectfully noted that the invention is directed to a composition and a composition that is formed by spray drying. Applicants appear to imply that the spray dried product of Miyajima may or may not be amorphous, and if this is the case, it may also raise the question whether applicants product is amorphous since the claimed product is formed/prepared by spray drying. Although, applicants argue that Miyajima mentions spray drying only once in the disclosure and as such cannot be relied upon for spray drying, it is the Examiner's position that there is a disclosure of spray drying in Miyajima. The claims are composition claims. Solidification in less than 5 seconds would be inherent since both the prior art and the claims spray dry. Also, the recitation of spray-dried particles solidifying in less than 5 seconds is not accorded patentable weight in a composition claim. However, both the prior art reference and the instant claims prepare the solid dispersions by spray drying. The claims are directed to compositions and the process of

preparing the dispersions in both the examined claims and the prior art are the same. Applicants provided no showing indicating that the particles of Miyajima solidified in longer than 5 seconds and there is no unexpected results showing that the dispersion of the prior art formed by spray drying as does the claimed invention differs in any way from the claimed solid dispersion.

Examiner recognizes that combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion can only establish obviousness, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, there is suggestion in Miyajima that the solubility of nifedipine, a poorly water-soluble drug, can be improved and Miyajima provides the how to process for improving drugs that are sparingly soluble.

The Declaration:

Applicants used several drugs including a drug having the closest structure to NZ-105, the conclusion from all the studies using the various drugs is that when the amount of the drug in the dispersion increased as the supersaturated concentration of dissolved drug decreases.

Response: The claimed invention in 1 is directed a composition comprising sparingly soluble water soluble drug and HPMCAS. The dose to aqueous solubility ratio of greater than 100 ml is a property of the drug or composition. Thus the declaration is not commensurate with the claims. It is respectfully noted that no specific drug is claimed in the rejected claims. Any sparingly water-soluble drug may have this property.

6. Claims 28-37 remain objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not teach composition comprising HPMCAS and glycogen phosphorylase inhibitors of claims 28-30 or the corticotropic releasing hormone inhibitors of claims 33-35 or the s-lipoxygenase inhibitor of claims 31 and 32 or antipsychotic of claims 36 and 37.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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